REMARKS

Reconsideration of the application is requested. The Specification has been corrected for an inadvertent typographical error. (A page showing the marking for the correction is attached hereto). Claims 36, 37, 42, and 45 have been cancelled without prejudice. Claims 35, 38, 40, 41, 44, 46, 47, 48, and 49 have been amended. (A page showing the markings for the changes made is attached hereto). Claims 53-72 have been newly added. No new matter has been introduced with this amendment which is fully supported by the Specification. Accordingly, claims 35, 38, 40, 41, 43, 44, 46-72 are now pending in this application.

The Examiner has made the restriction requirement final. Accordingly, the Group I claims directed to a G17-immunogenic composition are presently under examination on the merits. However, Applicant reserves the right to prosecute the claims of Groups II and III in a timely divisional application.

The Group I claims have been amended to more distinctly claim the instant invention. Thus, amended claim 35 is directed to an immunogenic composition formulated as an emulsion which is stable in frozen storage comprising an aqueous phase immunogen and a pharmaceutically acceptable oily vehicle selected from the group consisting of a Montanide type ISA 25, ISA 703, ISA 719, and ISA 720 without an additional emulsion stabilizer ; the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of the immunogen.

Amended claim 48 is directed to a method for formulating an immunogenic composition stable in frozen state comprising preparing an immunogenic emulsion by mixing an aqueous phase immunogen comprising an immunogenic carrier conjugated to an immunomimic peptide,

with a pharmaceutically acceptable oily vehicle so as to form a stable frozen storage oil-in-water or water-in-oil formulation wherein the oily vehicle is selected from the group consisting of a Montanide type ISA 25, ISA 703, ISA 719 and ISA 720 without an additional emulsion stabilizer, the thawed composition retaining at least 60% of the emulsion of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of the immunogen.

The newly added independent composition claim 53 is directed to an oil-in-water or water-in-oil emulsion which is stable in frozen storage comprising an aqueous phase immunogenic carrier conjugated to a G17 immunomimic peptide and a pharmaceutically acceptable oily vehicle consisting of Montanide type ISA 703, without an additional emulsion stabilizer; the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of the immunogen.

The independent method claim 62 is directed to preparing an immunogenic oil-in-water or water-in-oil composition which is stable in frozen storage by mixing an aqueous phase immunogen, comprising an immunogenic carrier conjugated to a G17 immunomimic peptide, with a pharmaceutically acceptable oily vehicle consisting of a Montanide type ISA 703 without an additional emulsion stabilizer; and the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of the immunogen.

The independent method claim 68 is directed to a method for stable frozen storage of an immunogenic emulsion comprising storing at a temperature ranging from –18°C to –80°C, an aqueous phase immunogenic carrier conjugated to an oily vehicle selected from the group consisting of a Montanide type ISA 25, ISA 703, ISA 719, and ISA 720 without an additional

emulsion stabilizer; the thawed emulsion retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of the immunogen.

The distinctive parameters of the claimed invention are supported throughout the description especially on pages 27, lines 7-10; p.12, line 6; and p. 22, lines 21 through 32.

Claim 35-37, 41-42 and 44 are rejected under 35 USC § 102(b) as being anticipated by U.S. 5,424,067 to Brancq et al. ("Brancq '067")

In the Examiner's opinion, the reference discloses a vaccine emulsion allegedly stable for over a year in storage at 4°C. The Examiner further contends that the claimed immunogenic composition may include additional compounds. The reference composition is stable in freezing temperature because of the inherent property of the reference squalene and squalane.

Applicant disagrees. The present invention is not anticipated, disclosed or even suggested by the cited Brancq '067 reference. The reference is silent on frozen storage of vaccine emulsions. Contrary to the Examiner's reading of the claimed invention and the cited reference, the claimed biphasic composition is either a water-in-oil or oil-in-water ruling out the cited reference's selection of only multiphasic w/o/w emulsion. The cited disclosure (Reference Examples 1-3) is actually teaching away from the instant biphasic system by declaring it as vaccine-ineffective, undesirably irritant and reactogenic (see Reference Example 4, Table 4-2). In fact, instant comparative tests showed that none of the W-O-W emulsions of the instant Specification was stable after e.g., -23°C and -70°C freeze-thaw cycling (5 cycles) (see Table 7, emulsion 4, 5, and 6).

Example 1 describes a comparison of IFA against another unnamed fluid mineral oil characterized as clear oil of straw yellow color prepared as multiphase emulsion BSA vaccine.

Example 2 describes a multiphase influenza vaccine using unnamed or identified mineral oil.

Example 3 allegedly composes efficacy and tissue intolerance of the multiphase type influenza vaccine emulsion to that of a w/o type. There is, however, no disclosure as whether the cited emulsion were stored over 12 months at 4°C before use for vaccination.

Example 4 also alleges improved tolerance to w/o/w mineral oil vaccine emulsion over the w/o emulsion type.

Ref. Table 5 (3408) shows the only example using an animal derived oil, namely saturated squalane. However, these droplets are allegedly observed under the microscope as a stable 1 μm size, not less 1 μm size. There are no w/o emulsion examples using metabolizable squalene.

As presently claimed, the instant composition provides for certain pharmaceutically acceptable oils but does not provide, in fact excludes, any additional emulsion stabilizing adjuvant. Contrary to the cited reference disclosure (Ref. Table 4-1, Table 5, etc.), the claimed emulsion does not contain added emulsion stabilizer beyond the particular oily vehicle content.

In contrast to the alleged long term 4°C storage stability of the reference emulsions, the presently claimed immunogenic emulsion is formulated to be stable in frozen storage and when thawed retains at least 60% of the emulsion at a globule size of less than 1 micrometer and exhibits a normal (that is: unaltered) immunogen release rate. Thus, the conformation and stability of the emulsion of the frozen-thawed emulsion is unpredictable from the prior art's alleged storage of over 12 months at +4°C.

Moreover, nowhere in Brancq '067 is there an actual disclosure of measuring retention of a globule size of less than 1 μm after a freezing-thawing cycle. There is no data or suggestion of the instant criterion of a stable emulsion as measured by the unaltered, i.e. normal release rate. There is no mention or suggestion in the cited reference that the stability of each example emulsion was measured after frozen storage of 12 months by any criteria, such as for example, the claimed criteria of globule size and immunogen release rate. Therefore, one of ordinary skill in this art would not reasonably predict, or even be motivated to try to test, that the alleged

stability at 4°C would inherently bring about stability of the composition by frozen storage, let alone after a freeze-thawing cycle.

Contrary to the Examiner's opinion, the stability of an oily vehicle at 4°C does not reasonably predict the impact of transition from unfrozen to frozen state and back to thawed or unfrozen state absent experimentation, since the aqueous component and the oily component of the emulsion freeze at different temperatures. On the contrary, one of ordinary skill in this art would expect the emulsion globules to coalesce when thawed thereby resulting in globules >1 μm. (see p. 6 line 32, through p. 7 line 1-5; p. 8 line 14-18). Applicant asserts that it is not the oily component alone such as the various suitable Montanide type ISA, that determines the stability of the emulsion upon freezing but it is its association with the aqueous phase solution which exerts an inter active effect by freezing and thawing at a different (lower) temperature range than the oily vehicle. Applicant wishes to point out that only certain pharmaceutically acceptable oily vehicle species have been found among those tested suitable for stable long-term frozen storage at temperatures ranging from -18°C to -80°C or multiple freeze/thaw cycling (p. 4. line 24-25; see also Table 7).

The cited reference is completely silent on the use of metabolizable animal-derived oil such as squalene. All the cited examples appear to show nonmetabolizable or poorly metabolizable mineral, synthetic, and saturated animal oils.

Applicant therefore asserts that the advantageous composition's retention of the immunogenic conjugate's purity or integrity after a freeze/thaw cycling (see support on page 18 of the Specification) is novel and unobvious over the cited disclosure. Moreover, the cited Brancq '067 reference is silent as to the preserved integrity of the conjugated antigenic constructs, after prolonged cold or frozen storage.

Finally, the cited reference discloses so many oily and emulsion stabilizing components that one of ordinary skill would be forced to conduct undue experimentation trying out combinations to find stable compositions stored at 4°C, let alone at any freezing temperature.

In view of the distinct and patentable difference of the present composition from the cited reference and the lack of teaching or suggestion therefor in the cited reference, reversal of the rejection of the claims under 35 USC § 102(b) is requested.

Claims 35-38, 41-42 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,109,026 to Hoskinson, et al. ("Hoskinson '026").

In the opinion of the Examiner, the cited reference discloses a vaccine emulsion of water-in-oil with LHRH or estrogen 17β-6 CMO conjugated to human serum albumin conjugate in saline and pharmaceutically acceptable squalene. The Examiner rejects claims 41-42, by alleging that the reference composition must be stable in cold or freezing storage because the inherent oily properties of squalene and squalane.

Applicant disagrees. On the contrary, the cited Hoskinson '026 reference does not anticipate, disclose or even remotely suggest the presently claimed invention.

In the first instance, Hoskinson '026 is silent on long term cold or frozen storage of the immunogenic emulsion as presently claimed. Moreover, the cited reference is completely silent as to the presently claimed stability criteria that the frozen-thawed composition retain at least 60% of the emulsion globules at a size of less than 1μm and exhibit a normal release rate of immunogen. There is no disclosure or even suggestion that the transition of the claimed composition from the thawed to the frozen and back to the thawed state would not reduce the high initial purity or integrity of the immunogenic conjugate or the desired emulsion globule size, as required for the presently claimed invention. Therefore, the evident stability of the instant emulsion preparations is not reasonably predicted or even suggested by the cited disclosure, particularly in the absence of additional emulsion stabilizers, as claimed.

In particular, the skilled artisan would expect that a freezing temperature as well as the thawing out would affect the aqueous phase component differently than the oily phase, due to different physical properties and unpredictable interphase relations between aqueous phase immunogen and oily layer. Thus, contrary to the Examiner's contention, the behavior or fate of

emulsion globules containing aqueous components which coexist in an oily continuous phase are not reasonably predictable after freezing as it relates to resistance against undesirable changes in globule size by coalescence into two separate phase layers so as to form undesirable large globule sizes (> 1 μm) as well as integrity or purity of the conjugated immunogenic constructs. Moreover, the reference is completely silent as to the instant criteria of integrity or intactness of the antigen constructs after emulsification, let alone prolonged cold storage.

In addition, as described in the instant Specification, not all but only some oily vehicle species were found unsuitable for frozen storage.

In view of these and the aforegoing arguments, Applicant asserts that the cited Hoskinson '026 reference does not claim, describe, or even suggest the presently claimed composition or method. The rejection is therefore deemed improper under the statute and should be withdrawn.

Claims 35-52 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,468,494. ("494"). The Examiner contends that the cited reference discloses the instant composition and method for preparing the same. In the Examiner's opinion, immunogenicity inherently increases due to the adjuvant character of "the reference mineral oil vehicle Montanide type ISA 703 in composition"; however, this adjuvant does not reasonably predict the improved immunogenicity of the vaccine composition after frozen storage.

Applicant disagrees. The cited '494 reference does not claim, disclose, or even suggest the frozen storage stability of the presently claimed immunogenic composition or preparation thereof. The cited patent discloses an aqueous solution containing the G17 peptide: DT conjugate together with or without nor-MDP adjuvant, containing AMS. Contrary to the Examiner's allegation, the reference Montanide type ISA 703 does not comprise "mineral oil", pharmaceutically acceptable, nontoxic, at least partially metabolizable, animal source oils, such as squalene and/or squalane.

Whereas the cited composition comprises an aqueous phase is mixed 1:1 with Montanide ISA 703 oily phase to which aluminum monostearate (AMS) is added as requisite emulsion stabilizer, the emulsion of the claimed composition does not contain any additional exogenous stabilizer. Moreover, the instant composition comprises Montanide ISA 703 mixed in the w/o emulsion at a 30/70 ratio.

In fact, the presently claimed composition, or the method claimed therefor, explicitly excludes the emulsion stabilizing additives beyond what is already included in the various suitable Montanide type ISA oily vehicle compositions. Moreover, the presently claimed Montanide ISA 703, formulation is not even suggested by the cited prior art as being suitable for frozen storage or stable after repeated freeze-thaw cycling, according to the criteria that at least

60% or alternatively at least about 97% of the emulsion retains a miniscule globule size of less than 1 μm and exhibits a normal (unaltered by storage) immunogen release rate. The instant emulsion retains a immunogen conjugate integrity of at least 91% after long term frozen storage and a freezing-thawing cycle.

The improved immunogenicity after frozen storage is deemed unobvious over the cited reference ('494).

Applicant asserts that the presently claimed composition, which does not contain the added stabilizer, e.g. AMS, is advantageously distinct and different from the '494 reference. The rejection under the statute should therefore be withdrawn, which favorable action is herewith solicited.

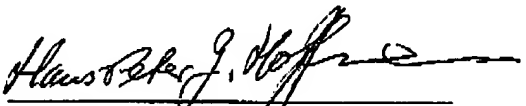
In view of the preceding amendment and remarks set forth thereto, Applicant believes the present claims are in allowable condition and therefore, respectfully requests reconsideration and withdrawal of all the rejections.

A good faith effort has been made to place this application in condition for allowance.

The Commissioner is hereby authorized to charge any fee which may be due in connection with this response to Deposit Account No. 23-1703.

Dated: March 24, 2003

Respectfully submitted,



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Enclosure

AMENDMENT: Version with Markings to Show Changes Made I.

IN THE SPECIFICATION:

On page 4, line 28, please replace "Analigunot" with --An aliquot--.

AMENDMENT: Version with Markings to Show Changes Made II.

IN THE CLAIMS:

35. (Amended) An immunogenic composition formulated as an emulsion which is stable in frozen [cold] storage comprising an aqueous phase immunogen and a pharmaceutically acceptable oily vehicle selected from the group consisting of the Montanide type ISA 25, ISA 703, ISA 719, and ISA 720, [comprising a suitable squalene or a suitable mixture of squalene and squalane]; without an additional emulsion stabilizer; the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of immunogen.

38. (Amended) The immunogenic composition as claimed in claim 35 [36], wherein the emulsion is formulated as a mixture of the oily vehicle and the aqueous phase immunogen so as to form an oil-in-water or water-in-oil emulsion.

40. (Amended) The immunogenic composition as claimed in claim 35 [36], wherein the oily vehicle is the Montanide ISA 703.

41. (Amended) The immunogenic composition as claimed in claim 35 or 66 [36], wherein the [cold] frozen storage can last at least one year.

44. (Amended) The immunogenic composition as claimed in [claim 36 or claim] anyone of the claims 35, 40, 41, 43, and 62, wherein the composition [exhibits] comprises significantly increased immunogenicity [upon storage] after one freezing-thawing cycle.

46. (Amended) The method as claimed in claim 48 [45], wherein the immunogen comprises a synthetic [hormone] immunomimic peptide conjugated to [or an effective fragment thereof combined with] an immunogenic component.

47. (Amended) The method as claimed in claim 46 or 48 wherein the peptide [hormone] comprises [is selected from the group consisting] an epitope of gastrin 17 (G17), gastrin 34 (G34), or [and] GnRH.

48. (Amended) A method for formulating an immunogenic emulsion stable in [cold] frozen storage [at freezing temperature] comprising:

preparing an immunogenic emulsion by mixing an aqueous immunogen comprising [a compound having] an immunogenic [portion] carrier conjugated to [and] an immunomimic [portion] peptide, with a pharmaceutically acceptable oily vehicle, so as to form a stable frozen storage oil-in-water or water-in-oil formulation, wherein the oily vehicle is selected from the group consisting of a Montanide type ISA 25, ISA 703, ISA 719 and ISA 720 without an additional emulsion stabilizer; the thawed composition retaining at least 60% of the emulsion at a globule size of less than 1 μm and exhibiting a normal release rate of the immunogen.

49. (Amended) The method as claimed in claim [45 or] 48, wherein the frozen storage stability of the immunogenic emulsion comprises a prolonged integrity of the immunogen.